Clinical manifestations, pathophysiology, treatment and outcome of inflammatory bowel diseases in older people

Butter, Matthias ; Weiler, Stefan ; Biedermann, Luc ; Scharl, Michael ; Rogler, Gerhard ; Bischoff-Ferrari, Heike A ; Misselwitz, Benjamin

Abstract: Approximately 10-20% of inflammatory bowel disease (IBD) cases are diagnosed after 60 years of age. Due to the high prevalence of conditions mimicking IBD at older age - including bowel disease associated with non-steroidal anti-inflammatory drugs, diverticulitis, and microscopic colitis - differential diagnosis of IBD among older adults is frequently delayed. Late-onset IBD is characterized by a predominance of colonic disease and an overall milder disease course; disease progression and new intestinal manifestations are rare. However, older patients are less able to tolerate inflammation and their risk of mortality from severe disease is increased. Management of late-onset IBD has been insufficiently studied since older adults are underrepresented in clinical trials and specific problems of older patients such as incontinence have not been addressed. To date, treatment generally follows the same principles as in the younger. However, older patients are at higher risk of severe adverse effects of the disease and its treatments, including bone and muscle loss, infections and lymphoma. Therefore, the safety profile of a given drug is of paramount importance in older patients with IBD. Colectomy with ileo-anal pouch anastomosis for refractory ulcerative colitis can be performed safely, although functional results may be inferior to those in middle-aged patients. To decrease mortality among older patients, a timely surgical intervention is important. Patients with late-onset IBD frequently develop colorectal carcinoma within 8 years of diagnosis; therefore, colorectal cancer screening immediately after diagnosis should be considered. Further, the clinical care of older patients with IBD needs to extend to overall health, including nutrition, vaccination, bone, muscle and mental health.

DOI: https://doi.org/10.1016/j.maturitas.2018.01.015

Clinical manifestations, pathophysiology, treatment and outcome of older people with inflammatory bowel diseases

Matthias Butter[1], Stefan Weiler[2], MD, Luc Biedermann[1], MD, Michael Scharl[1], MD, Gerhard Rogler[1], MD, PhD[1], Heike A. Bischoff-Ferrari[3], MD, Benjamin Misselwitz[1], MD

[1]Division of Gastroenterology and Hepatology, University Hospital Zurich (USZ) and Zurich University, Zurich, Switzerland

[2]Department of Geriatrics and Aging Research, University Hospital Zurich (USZ) and Zurich University, Zurich, Switzerland

[3]Division of Clinical Pharmacology and Toxicology, University Hospital Zurich (USZ) and Zurich University, Zurich, Switzerland

Running title: IBD in older adults

Key words: Inflammatory bowel disease, seniors, elderly patients, Crohn's disease, ulcerative colitis, TNF-inhibitors, integrin inhibitors

Abbreviations: CD: Crohn's disease, IBD; inflammatory bowel disease, TNF: tumor necrosis factor, UC: ulcerative colitis

Funding: This research was supported by a grant from the Swiss National Science Foundation to BM (Grant No. 32473B_156525)

Please address correspondence to:

PD Dr. med. Benjamin Misselwitz
Division of Gastroenterology and Hepatology
University Hospital Zurich and Zurich University
Rämistr. 100
8091 Zürich
Switzerland
benjamin.misselwitz@usz.ch

Abstract

Approximately 10-20% of inflammatory bowel disease (IBD) cases are diagnosed beyond 60 years of age. Due to the high prevalence of conditions mimicking IBD at older age including NSAR bowel disease, diverticulitis, microscopic colitis differential diagnosis of IBD among senior adults is frequently delayed.

Late-onset IBD is characterized by predominance of colonic disease and an overall milder disease course with rarer disease progression or new intestinal manifestations. However, senior patients are less able to tolerate inflammation and their risk of mortality with severe disease is increased.

Management of late-onset IBD has been insufficiently studied since senior adults are underrepresented in clinical trials and specific problems of older patients such as incontinence have not been addressed. To date, treatment generally follows the same principles as in the younger. However, older patients are at higher risk for severe adverse effects of the disease and its treatments, including bone and muscle loss, infections and lymphoma. Therefore, the safety profile of a given drug is of paramount importance in senior IBD patients. Colectomy with ileo-anal pouch anastomosis for refractory ulcerative colitis can be performed safely, although functional results may be inferior compared to middle-aged patients. To decrease mortality among senior patients, a timely surgical intervention is important.

Late-onset IBD patients develop colorectal carcinoma frequently within the first 8 years after IBD diagnosis; therefore, colorectal cancer screening immediately after diagnosis should be considered. Further, clinical care for senior IBD patients needs to extend to overall health including nutrition, vaccination, bone, muscle and mental health.

Introduction

Crohn`s disease (CD) and ulcerative colitis (UC) are manifestations of chronic intestinal inflammation. Awareness of inflammatory bowel diseases (IBD) in senior adults has been increasing and a number of reviews addressed this subject [1-8]. The definition of „senior adults“ or “elderly” varies between ≥50 and ≥65 years; however, a cut-off of 60 years has been most commonly used [2].

IBD in senior patients comprises senior patients with a new IBD diagnosis (“late-onset IBD”) and patients with juvenile or adult onset IBD reaching advanced age. Most systematic studies focus on late-onset IBD and senior patients with long-standing IBD remain poorly studied. Due to the imminent demographic change with a growing segment of senior adults, a significant rise in older IBD patients is expected [2].

Today, 10-20% of new IBD diagnoses occur in senior adults age >60 years [2, 9]. Population based studies found a worldwide incidence of 4-6 per 100,000 per year in CD and 5-8 per 100,000 per year UC in adults >60 years [10, 11]. A recent Dutch population based cohort reported even higher numbers with an increase of late-onset IBD from 11.7 to 23.7 per 100.000 between 1991 and 2011 [12].

A bimodal age distribution with a first peak at approximately 25 years and a second peak beyond 60 years has been reported for the incidence of CD and UC in population-based studies and hospitalization statistics [13-15]. These two peaks might reflect exposure to two different categories of IBD risk factors [13]. However, only a third of all studies confirmed such a bimodal distribution [11] and misclassification of IBD might contribute to late-onset IBD [1].

Presentation and clinical course

Late-onset IBD is characterized by a predominance of colonic disease and a generally milder presentation [8, 16, 17]. In line with colonic predominance, for individuals with IBD, older age is associated with the diagnosis of UC [18]. For UC, left-sided disease was more frequent than the more severe pancolitis (OR: 1.5) [2].

In keeping with colonic predominance, late onset CD more likely manifests as colonic disease (OR 2.6, CI: 1.9-3.5) and less likely as ileocolonic (OR 0.43) [2]. Late-onset Crohn’s disease is associated with a benign inflammatory disease course; a penetrating (fistulizing) course was less frequently observed (OR: 0.48) [2]. Perianal involvement was also less frequently described (OR 0.64) in most [2, 12, 19] but not all studies [16].

Late IBD is typically non-progressive: An increase in disease extent over time was observed in only 16% of UC patients in a French population based cohort [16], compared to almost 50% progression in pediatric cohorts [3]. Similarly, no new intestinal manifestations occurred in 92% of patients with CD over time [16].

The prognosis of late-onset IBD is controversial and initial studies reporting increased mortality have been challenged. One illustrative study from a tertiary care hospital reported a higher rate of steroid free-remission at 1 year in UC patients ≥50 years compared to younger individuals (64% vs. 49%) [20]. However, hospitalized senior IBD patients remain a high risk population with a higher mortality compared to younger patients (OR 3.9), even after adjusting for co-morbidities [21].

Fecal incontinence predominantly affects senior IBD patients and can greatly affect performance, self-esteem and quality of life. Fecal incontinence was reported in 20%-25% of patients with IBD [22, 23]; however, in a survey as many as 74% of respondents reported some degree of incontinence [24]. Risk factors for incontinence include older age, female gender, liquid stools, perianal disease and previous

Kommentiert [BM1]: Additional reference

Kommentiert [BM2]: Additional reference{Ha, 2013 #211}

Kommentiert [BM3]: Additional reference

Kommentiert [BM4]: Additional reference

Kommentiert [BM5]: revised

Kommentiert [BM6]: additional reference

colorectal and perianal surgeries but not IBD diagnosis (UC or CD) [22-24]. Therefore, in senior adults with IBD and mild intestinal inflammation, stool incontinence might be the predominant symptom. Notably, stool incontinence is frequently not mentioned by patients and active inquiry is advisable. Further, abdominal pain might be reported less frequently in senior IBD patients [16].

Differential diagnosis

The diagnostic delay for CD is 6 years in senior adults compared to 2 years in younger individuals [10]. This difference might be caused by a high number of alternative diagnoses with a high incidence in senior adults including diverticulitis, microscopic colitis, ischemic bowel disease, non-steroidal anti-inflammatory drug (NSAID)-associated colitis and infectious colitis including *Clostridium difficile* colitis [1, 9, 25]. This high number of differential diagnoses represents the most likely explanation for the high rate of misdiagnoses of IBD at initial presentation (60% vs. 15% in younger patients) [1].

Kommentiert [BM7]: additional reference

Pathophysiology

IBD pathophysiology likely comprises yet poorly characterized interactions of genetic changes and environmental factors with the gut microbiota and the intestinal immune system (Figure 1). In young IBD patients, genetic factors are of greater importance than in senior patients [17, 26, 27]. In a French population-based study, a family history of IBD was presented in 13% of patients <17 years vs. 3% of individuals >60 years [16]. Among CD patients, individuals with the highest genetic risk developed CD 5 years earlier than individuals with the lowest risk [28].

Kommentiert [BM8]: Additional reference

Vice versa, in senior IBD patients, environmental factors are likely of paramount importance. Smoking is the best-studied environmental factor in IBD and quantitative tobacco smoke exposure is a strong risk factor for severe disease with multiple surgeries in CD patients [29]. In contrast, smoking cessation is a risk factor for UC and a severe disease course. In Switzerland, overall smoking rates of IBD patients paralleled the Swiss population with a higher fraction of smokers in CD than UC (40% vs. 15%) [30]. Smoking rates tend to decrease in the general population and significant fraction of senior adults will have succeeded in smoking cessation, potentially explaining a fraction of elderly-onset UC cases [20]. Exposure to height >2000 m or long-term air travel have been suggested as risk factors of an IBD flare [31] and might be more prevalent in the younger. Additional environmental factors with differential exposures in senior IBD patients include NSAID, antibiotics, diet, vitamin D, sleep, hygiene and air and water pollution [32].

The gut microbiota undergoes profound changes upon aging, and age-dependent microbiota changes have been associated with frailty [33-35]. Moreover, recent antibiotic therapies were risk factors for a subsequent IBD diagnosis in adult and pediatric patients with the highest risk in individuals with multiple antibiotic therapies [36-38]. Senior patients are at risk for both, recent antibiotic treatment and high lifetime cumulative antibiotic exposure. These iatrogenic microbial alterations might result in an imbalanced microbiota composition ("dysbiosis") as a pre-requisite for IBD [36, 37]. Age-dependent changes in physiology with lower intestinal motility with slower transit time, constipation and fecal retention, shifts in gastric pH, decreased nutrient intake and lower physical activity might also contribute to dysbiosis [4].

Kommentiert [BM9]: Additional references

Immunosenescence, referring to age-dependent changes in the immune system, is most pronounced in the adaptive immune system[39]. Upon regression of the thymus, the number of naïve T cells and the diversity of the T cell receptor repertoire decreases. This results in a lower plasticity of the immune system and a decreased response to infection [40]. On the other hand, the number of terminally

differentiated ("senescent") T cells increases. These cells are activated by autologous antigens or microorganisms including cytomegaly virus [41]. Similarly, in the B cell system antibody production and response to antigens are reduced, accompanied by an increase of antigen-experienced, terminally differentiated and pro-inflammatory (senescent) B cells [42].

Immunosenescence also includes pro-inflammatory changes in the innate immune system with a higher number of neutrophils and changes in the natural killer cell system [40, 42]. The contribution of the pro-inflammatory state of the aging immune system ("immune-aging") to IBD pathogenesis is not understood but remains a potential target for future IBD therapies for senior patients.

Treatment

IBD treatment for senior patients follows the same principles as treatment for the younger and no specific guidelines exist [43-45] (Figure 2). Several key points need to be emphasized: i) Less systematic knowledge is available since seniors adults have been systematically excluded from clinical trials [9]. ii) Senior patients are less able to tolerate severe and lasting inflammatory IBD activity. In addition, elderly patients iii) will more likely experience complications from IBD including thromboembolism and cancer, iv) are more likely to experience side effects of any treatment and v) co-morbidities and drug-drug interactions limit therapeutic options.

Balancing benefits and safety issues of any treatment is a specific challenge during the care of senior patients. Due to the more benign clinical course and the low likelihood of disease progression, prognostic interventions for IBD are much less of a concern in senior adults. Therapy should instead focus on immediate medical needs and functionality in the activities of daily living.

In senior patients, comorbidities and polypharmacy are prevalent with an increased risk for drug-drug or drug-disease interactions (Table 1) [5, 43, 46]. In one study, IBD patients ≥65 years were treated with an average of 9 different medications. 74% of individuals were at risk for potential medication interactions including 40% with interactions with IBD medication [47].

Kommentiert [BM10]: Additional reference

Age-dependent changes in liver and renal function and body composition can also impair pharmacokinetics. Volume of distribution of substances can be altered by age-related increase of body fat and reduction of total body water, lean muscle mass and hypoproteinemia. Decreased liver and renal function in the elderly increase the risk for accumulation of drugs and metabolites. For instance, the systemic bio-availability of budesonide of 10-15% is increased in senior adults with a higher likelihood of systemic adverse effects [48].

Susceptibility to specific adverse drug reactions can be increased in senior patients due to co-morbidities such as metabolic syndrome or cardiovascular diseases (Figure 2, Table 1). Infections in seniors under immunosuppressive therapy can take a more serious clinical course and due to age-related alterations of natural barriers and immune-aging (see above). Long-term immunosuppressive treatment contributes to malignancy [49] including non-melanoma skin cancer [50] or hematologic malignancies, such as lymphomas [51].

Kommentiert [Office11]: Ist this true?

Kommentiert [BM12R11]: Yes –> See reference

Aminosalicylates

Oral and topical 5-Aminosalicylic acid (5-ASA) are highly effective as an induction and maintenance therapy for UC [43, 52, 53]. In contrast, 5-ASA in the treatment of CD is less effective for maintenance of remission . In a recent population based French cohort study, 5-ASA was the most frequently prescribed IBD treatment for the elderly and 80% of CD as well as 84% of UC patients had been treated

Kommentiert [BM13]: Additional reference

Kommentiert [BM14]: Additional refrence

with 5-ASA within 10 years after diagnosis [16, 17]. Overall, 40-60% of senior UC patients adhere to 5-ASA treatment [4]. The high frequency of 5-ASA use in senior adults might be explained by excellent tolerability and limited safe alternatives. Pill size and number as well as problems with self-administration of suppositories, enemas and foams limit 5-ASA usage in some patients [43, 56].

Kommentiert [BM15]: New reference

Corticosteroids

Corticosteroids are usually required for the induction of treatment in UC, not responding to 5-ASA and moderate to severe flares of CD. In population based studies, 47-63% of senior CD patients and 40-58% of senior UC patients received systemic steroids within 5-10 years after diagnosis [12, 16, 17, 57]. However, steroids are limited by dose- and duration-dependent adverse effects such as osteoporosis and sarcopenia, contributing to frailty and loss of autonomy among senior patients. In Swiss IBD patients, steroids (OR 4.4) and age (OR 1.03 per year) were the most relevant risk factors for decreased bone mineral density [17, 58].

Kommentiert [BM16]: New reference

Kommentiert [BM17]: Additional reference

Thiopurines

Immune-suppressive thiopurines (azathioprine and 6-mercaptopurine) are frequently used in elderly IBD patients (31-60% in CD, 15-25% in UC, respectively [12, 16, 57]). Side effects include dose-dependent myelosuppression, necessitating regular blood tests every 3 months. Treatment of gout with allopurinol/ febuxostat severely exacerbates this risk [59]. Use of thiopurines >1 year increases the risk of malignancies such as lymphoproliferative disorders (HR 6), non-melanoma skin cancer (HR 2.5-7) and bladder cancer in males (HR 6) [49]. Age (OR 1.8 per decade) and male gender (OR 4.1) are additional risk factors for lymphoma [60]. Combination of thiopurines with tumor necrosis factor (TNF)-inhibitors further exacerbates lymphoma risk (HR 2.35) including aggressive hepatosplenic T-cell lymphoma [43, 51, 61-63]. However, despite the risk of malignancy, thiopurines are appropriate for senior patients with moderate-to-severe IBD but continuation of therapy should be evaluated after 1 year [43]. Methotrexate might be an alternative but no specific data for senior IBD patients are available.

Kommentiert [BM18]: Revised references

Tumor necrosis factor (TNF)-inhibitors

TNF-inhibitors are a cornerstone of contemporary IBD therapy. Benefits include induction of remission, improved quality of life and decreased hospitalizations or surgery. Whether senior patients respond differently to TNF-inhibitors remains unclear. Two studies reported older age as a significant risk factor for suboptimal response [64, 65]. Furthermore, rates of discontinuation of therapy were two-fold higher in senior IBD patients [66].

Older age is also a significant predictor for severe adverse events upon anti-TNF treatment. In patients older than 65 years, the incidence of severe infections and total mortality was 11% and 10%, respectively, compared to 2.6% and 1% in younger patients [43, 67]. Co-morbidities, such as severe liver disease, hematological disorders and congestive heart failure, also limit usage of TNF-inhibitors. Perhaps not surprisingly, TNF-inhibitors were rarely used in senior IBD patients with cumulative treatment rates of 5% in CD and 2% in UC over a 5-year observation period in population-based cohorts [16, 57]. However, a Dutch cohort reported higher treatment rates of 34% in CD and 9% in UC [12].

In summary, for senior patients with moderate-to-severe CD or UC, TNF-inhibitors are an effective treatment option with an acceptable safety profile, provided continuous monitoring for infection and other adverse effects can be provided [43, 68].

Integrin inhibitors

Inhibitors of integrin α4β7, such as vedolizumab, prevent homing of immune cells into the intestine. Vedolizumab is effective for induction and maintenance of remission in CD and UC. In line with the gut-specific mechanism, the safety profile of vedolizumab is excellent with a modest increase of gut and upper airway infection rates as the main adverse effects. Studies of vedolizumab included only low numbers of individuals >55 years (130 out of 895 participants; 15%), but a recent post-hoc analysis reported safety of senior adults included in these trials [69]. Provided future trials confirming safety and effectivity for the elderly, integrin inhibitors might become the treatment of choice in this patient group.

Ustekinumab

Ustekinumab has recently been introduced for the treatment of CD [70]. Specific data for the elderly are lacking; however, the excellent safety profile renders ustekinumab a promising drug for senior adults.

Cyclosporine

Cyclosporine is a rescue treatment for severe or fulminant disease in IBD patients. Due to adverse effects including renal insufficiency and infection for which the elderly are at higher risk, cyclosporine remains an option of last resort in senior adults [43].

Surgery

Surgery represents a key element of IBD therapy in patients with failure of or intolerance to medical treatment. Population based cohort studies of senior IBD patients reported surgery rates of 32-33% for CD and 8% for proctocolectomy in UC [12, 16]. In a Canadian study surgery rates were 24% in CD and 12% in UC upon 5-year follow-up [71].

In UC, proctocolectomy with ileo-anal pouch anastomosis is now the surgical treatment of choice for young and senior adults. Even though 90% of elderly UC patients are overall satisfied with the surgical outcome [72], results are less favorable beyond age 65 compared to younger individuals [7]. After surgery, senior adults experience higher rates of incontinence, pouchitis and anastomotic strictures [7, 73]. The mortality of elderly UC patients undergoing elective surgery is now <3% [74]; however, adequate patient selection and education remain critical [1]. Treatment principles for CD surgery do not differ in young and older individuals but the probability of disease recurrence rates after CD surgery is controversial [1, 75].

Timing of surgical treatment is decisive in IBD patients [1, 75] and delaying surgery is poorly tolerated in senior adults. Mortality upon emergent UC surgery can be as high as 27% [8, 76]. Therefore, age should not be a reason to delay surgery.

Kommentiert [BM19]: Additional reference

Kommentiert [BM20]: Additional reference

Healthcare maintenance

Healthcare maintenance comprises interventions to prevent illness and promote fitness and health. In IBD patients, several preventive interventions are recommended (Table 2) [77-79]. However, in one British American study, IBD patients received preventive services at a lower rate compared to control individuals [80]. Clear communication between patient, primary care physician and gastroenterologist about these shared responsibilities might improve the frequency of vaccination and other effective interventions in elderly IBD patients [78].

Kommentiert [BM21]: Additional reference

Symptoms of depression and anxiety are prevalent in 22% and 35% of IBD patients, respectively [81]. Psychotherapy and pharmacotherapy are efficient also in IBD patients [82]. Depression is more common in senior adults but frequently goes undetected even though treatment options exist [83]. Therefore, informal or formalized screening regarding quality of sleep, mood, anxiety, energy level and ability to experience joy is strongly advised.

Osteoporosis and osteoporotic fractures are increased by 40-60% in IBD patients [84, 85]. Senior IBD patients are at increased risk of osteoporosis and related fractures due to malnutrition, vitamin D deficiency and reduced physical activity [58, 86]. Given this risk profile in addition to age-related bone loss, Dual Energy X-ray Absorptiometry (DXA)-screening among senior IBD patients with steroid exposure and/or additional risk factors is recommended [52, 86]. However, recent data indicate an inconsistent implementation of osteoporosis screening and treatment even in countries with a developed health-care system [87].

Malnutrition is more prevalent in IBD patients >65 years compared to the younger [21]. In addition, deficiency of vitamin D (11% in CD, 18% in UC), vitamin B12 (18% CD, 17% UC) and iron (13% CD, 20% UC) were found in senior IBD patients in an illustrative study [88]. Therefore, an annual assessment of diet, body weight and a laboratory including albumin, ferritin, 25-hydroxyvitamin D and vitamin B12 is warranted [77].

Colorectal cancer screening

IBD can be complicated by malignancy and most malignancies and malignancy-related deaths occur in patients ≥65 years [49, 75]. Colorectal cancer (CRC) screening is advised in all individuals beyond age 50. However, for IBD patients, a first screening colonoscopy is recommended 8 years after onset of IBD symptoms [89]. However, in a population-based Dutch study, in senior patients 35% of CRC cases developed within 8 years after IBD diagnosis, before the recommended onset of screening. Age at diagnosis was a significant risk factor for these early-onset CRC (HR 2.25 for 10-year older age) [90]. Furthermore, a large study form Hong Kong described a much shorter interval to diagnosis of flat dysplasia in late-onset IBD patients (1 years vs. 8 years in younger patients) [91]. These data illustrate a specific risk for CRC in elderly-onset IBD patients and an additional screening colonoscopy 1-2 years after onset of IBD symptoms seems warranted. Surveillance colonoscopies at high frequencies should subsequently be performed in individuals with risk factors including family history of CRC, severe and extensive colitis, past dysplasia or primary sclerosing cholangitis (PSC) [89].

Kommentiert [BM22]: Additional reference

Kommentiert [MB23]: Additional reference

Kommentiert [MB24]: Additional reference

Conclusion

In summary, late-onset IBD comprises 10-15% of all IBD patients. While the disease course remains generally mild, a minority of high-risk patients with severe disease exists which requires aggressive

management. Challenges include an accurate diagnosis, a patient centered symptom directed therapy, and healthcare maintenance issues such as cancer surveillance.

Methods

Search strategy: We performed a Medline search with the following strategy: (IBD OR inflammatory bowel disease OR Crohn's disease OR Crohns disease OR Morbus Crohn OR ulcerative colitis OR Colitis ulcerosa) AND (older people OR elderly OR elderly-onset OR elderly onset OR old patient OR elderly patient OR IBD in elderly OR IBD in older patient OR IBD in old patients) AND (management OR differences OR treatment OR therapy OR physiology OR phenotype OR guideline); The search was limited to English language with a publication date after 2006 and filtered for Clinical Trials, Reviews, Guidelines, Meta-analyses, and systematic reviews. Another Medline search using identical search terms with less limitations regarding type of article (only excluding case reports) was performed for the years 2016 and 2017.

Our search revealed 1547 publications which were screened. All articles potentially providing information regarding epidemiology, pathophysiology, clinical presentation and management of IBD in the elderly were retrieved and screened for relevance (207 articles). Due to space limitations only 26 articles were finally used and quoted in the manuscript.

Author contributions

MB and BM designed the review and wrote the first draft of the paper, LB, MS, GR, SW and HBF revised the paper for important intellectual content. All authors approved the final version of the manuscript.

Tables and Figures

Drug class / category	**Substances**	**Common drug reactions** **Severe adverse reactions**	**Drug-drug interactions**	**Precautions and recommendations in specific susceptible populations**
Aminosalicylate	5-aminosaliclic acid (5-ASA, mesalamine)	- Abdominal pain, diarrhea, nausea, vomiting, arthralgia, asthenia - Renal impairment, gastrointestinal hemorrhage, cytopenia, pancreatitis	- NSAID: increased risk of bleeding - Thiopurines: increased risk of myelosuppression	- Monitoring of laboratory parameters (blood count, renal function
Corticosteroids	Prednisone Budesonide (better tolerated due to first path effect in liver)	- Osteoporosis, hypertension, impaired glucose tolerance - Impaired wound healing, Cushing's syndrome, gastrointestinal perforation, aseptic necrosis of bones, risk for infections, adrenal insufficiency, glaucoma, depression, delirium - More pronounced adverse events in senior patients	- NSAID: increased risk of gastrointestinal bleeding - CYP3A4 inhibitors: concentration and effect increased with risk of e.g. Cushing's syndrome, hypertension, adrenal suppression - Quinolones: risk of tendon rupture	- Gradual dose reduction if risk for adrenocortical insufficiency - Aim for usage <3 months - Clinical monitoring (blood pressure, myopathy, ophthalmological) - Laboratory monitoring (glucose) - Osteoporosis screening using bone densitometry - In senior patients close monitoring is advised
Thiopurines	Azathioprine 6-Mercaptopurine	- Nausea, vomiting - Hematotoxicity, hepatotoxicity, infections, pancreatitis, malignancy risk (especially in senior patients)	- Allopurinol, febuxostat: increased thiopurine toxicity with severe myelosuppression. Combination only under strict restrictions and surveillance! - ACE inhibitors: myelosuppression	- Yearly screening for dermatologic malignancies - Monitoring of laboratory parameters: blood count, liver function test (e.g. 1 month after dosage change, 3 months)

			- Echinacea: decreased effectiveness of thiopurines	- Hypersensitivity cross-reaction between different thiopurines - Close monitoring in senior patients
Calcineurin inhibitor	Cyclosporine	- Hypertension, gingival hyperplasia, tremor - Hepatoxocity, nephrotoxicity, infections - poorly tolerated in senior patients	- Selected statins: contraindicated due to increased risk of myopathy and rhabdomyolysis - NSAID: nephrotoxicity - CYP3A4 inhibitors: increased cyclosporine concentrations and toxicity - TNF-inhibitors: decreased concentrations, reduced effectiveness	- Close therapeutic drug monitoring in combination with CYP inhibitor/ inducer - Monitoring of drug levels and renal function - Extreme caution in senior patients
TNF-inhibitors	Infliximab Adalimumab Golimumab Certolizumab	- Headache, fatigue, upper respiratory infections, rash, nausea - Anaphylaxis, opportunistic infections, malignancy, autoimmune hepatitis, acute liver failure, heart failure	- Other immunosuppressants: increased risk for infections and malignancy (especially in senior patients)	- Tuberculosis (tuberculin skin test (TST) and/or interferon-gamma release assay (IGRA),) and HBV testing prior to initiation - Avoid in heart failure; worsening of symptoms possible - Laboratory monitoring (blood count, liver function tests) - Caution in senior patients
Integrin inhibitors	Vedolizumab	- Arthralgia, nausea, upper respiratory infections, fatigue - Hepatitis, anaphylaxis, PML, infections	- TNF-inhibitors, cave with combination due to potentiation of immunosuppression - Echinacea: decreased effectiveness of vedolizumab	- Live vaccination prior to initiation - Laboratory monitoring (liver function)
Anti-IL12 and anti-IL23	Ustekinumab	- Upper respiratory and urinary tract	- TNF-inhibitors: cave with combination due	Live vaccination, (e.g. BCG <1 year

monoclonal antibody		infections, fatigue, headache, vomiting - Skin cancer, anaphylaxis, PRES, serious infections	to potentiation of immunosuppression	prior to initiation, during, or <1 year after discontinuation of ustekinumab is not recommended

Table 1. Drug classes, example of substances, selected adverse drug reactions and drug-drug interactions pronounced in the elderly.

CYP3A4 inhibitors: Cytochome P450 isoenzyme 3A4 inhibitors: ciprofloxacin, clarithromycin, erythromycin, fluconazole, itraconazole, posaconazole, voriconazole; fluvoxamine; amiodarone, ceritinib, cobicistat, cyclosporine, darunavir. CYP3A4 inducers exhibit opposite effects with reduced substrate concentrations and effectiveness. HBV hepatitis B virus. PML progressive multifocal leukoencephalopathy. PRES posterior reversible encephalopathy syndrome. BCG Bacillus Calmette-Guierin. TNF: tumor necrosis factor. ACE: angiotensin converting enzyme. IL: Interleukin

Intervention	Comments
Vaccination	Follow guidelines for elderly individuals • Influenza, pneumococcal, herpes zoster vaccines among others Avoid life vaccines in the immune-suppressed patient*
Colorectal cancer screening	Colonoscopy screening every 10 years, starting at age 50 years. Additional screening should be considered in high-risk individuals. Elderly-onset IBD patients might be a high-risk population for CRC and additional screening starting 1-2 years after diagnosis should be considered.
Skin cancer screening	In immune-suppressed individuals yearly skin inspection by dermatologist
Mental health	Structured inquiry regarding • Quality of sleep • Mood, level of energy • Did patient stop enjoying pleasant activities
Bone health	In IBD patients with long and/ or severe inflammation and/ or steroid usage or additional risk factors • DXA scan • If appropriate calcium and vitamin D supplementation
Malnutrition	Informal inquiry about nutrition, eating habits Documentation of weight at regular intervals Measure albumin, ferritin, vitamin D, vitamin B12 and folic acids at least yearly
Smoking cessation	High benefits also for senior patients Regular counselling, refer to smoking cessation program Senior patients: Less likely to start quitting, but higher changes for success

***Table 2**: Health maintenance in senior IBD patients, recommended interventions and comments.*

*Live vaccines include: adenovirus, rotavirus, Bacille Calmette-Guerin (BCG), live attenuated (intranasal) influenca, live attenuated poliovirus, measles, mumps, rubella, varicella, zoster, smallpox, oral typhoid and yellow fever vaccine.

Figure Captions

***Figure 1*: Risks and relevant physiological changes in senior IBD patients.**

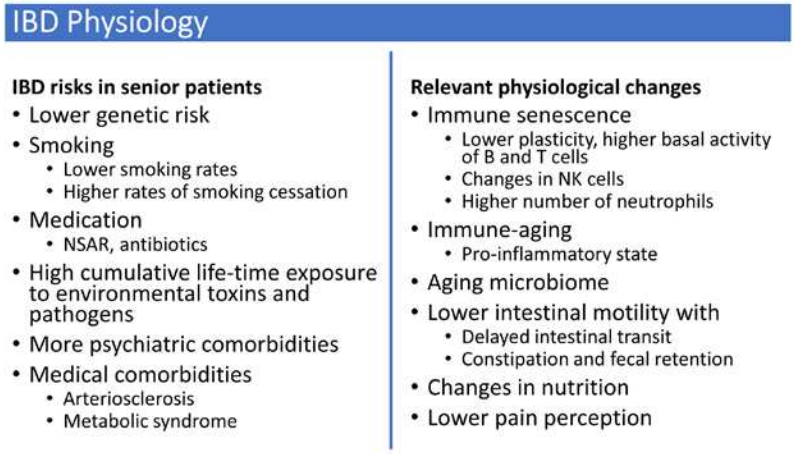
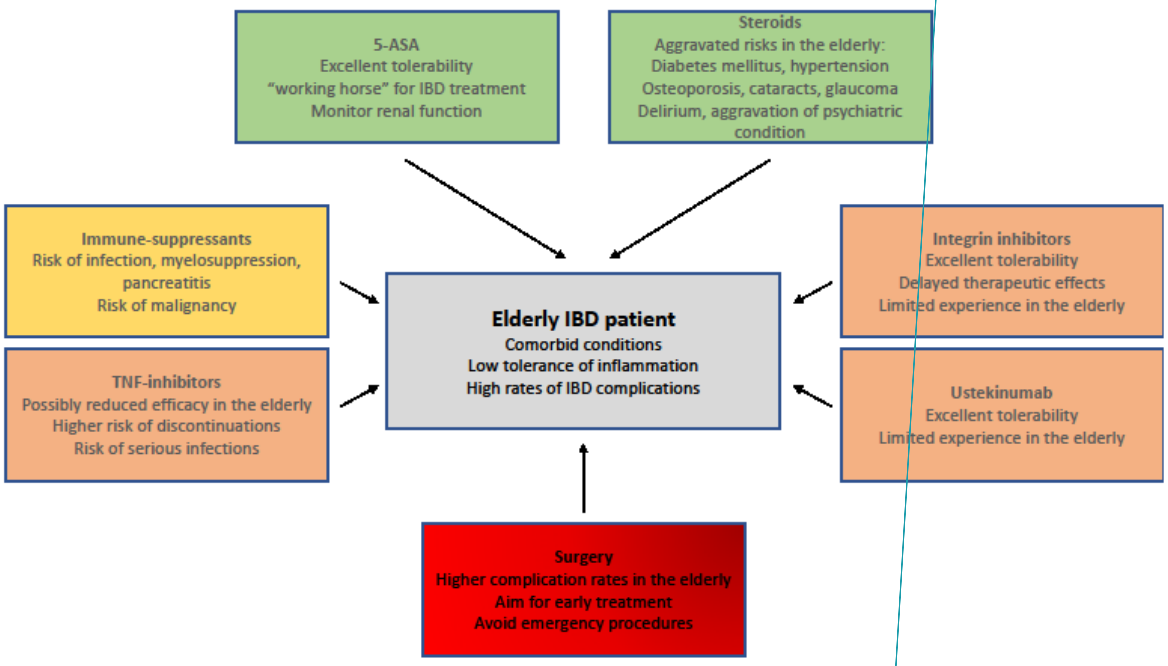


***Figure 2:* Overview of therapeutic options for elderly IBD patients.**

Feldfunktion geändert



References

1. Gisbert, J.P. and M. Chaparro, *Systematic review with meta-analysis: inflammatory bowel disease in the elderly.* Aliment Pharmacol Ther, 2014. **39**(5): p. 459-77.
2. Ananthakrishnan, A.N., et al., *Systematic Review and Meta-analysis: Phenotype and Clinical Outcomes of Older-onset Inflammatory Bowel Disease.* J Crohns Colitis, 2016. **10**(10): p. 1224-36.
3. Duricova, D., et al., *Age-related differences in presentation and course of inflammatory bowel disease: an update on the population-based literature.* J Crohns Colitis, 2014. **8**(11): p. 1351-61.
4. Taleban, S., et al., *Inflammatory bowel disease and the elderly: a review.* J Crohns Colitis, 2015. **9**(6): p. 507-15.
5. Ha, C.Y. and S. Katz, *Clinical implications of ageing for the management of IBD.* Nat Rev Gastroenterol Hepatol, 2014. **11**(2): p. 128-38.
6. Ruel, J., et al., *IBD across the age spectrum: is it the same disease?* Nat Rev Gastroenterol Hepatol, 2014. **11**(2): p. 88-98.
7. del Val, J.H., *Old-age inflammatory bowel disease onset: a different problem?* World J Gastroenterol, 2011. **17**(22): p. 2734-9.
8. Stepaniuk, P., et al., *Characterization of inflammatory bowel disease in elderly patients: A review of epidemiology, current practices and outcomes of current management strategies.* Can J Gastroenterol Hepatol, 2015. **29**(6): p. 327-33.
9. Katz, S. and D.S. Pardi, *Inflammatory bowel disease of the elderly: frequently asked questions (FAQs).* Am J Gastroenterol, 2011. **106**(11): p. 1889-97.
10. Katz, S. and R. Feldstein, *Inflammatory bowel disease of the elderly: a wake-up call.* Gastroenterol Hepatol (N Y), 2008. **4**(5): p. 337-47.
11. Molodecky, N.A., et al., *Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review.* Gastroenterology, 2012. **142**(1): p. 46-54 e42; quiz e30.
12. Jeuring, S.F., et al., *Epidemiology and Long-term Outcome of Inflammatory Bowel Disease Diagnosed at Elderly Age-An Increasing Distinct Entity?* Inflamm Bowel Dis, 2016. **22**(6): p. 1425-34.
13. Sonnenberg, A., *Age distribution of IBD hospitalization.* Inflamm Bowel Dis, 2010. **16**(3): p. 452-7.
14. Kurata, J.H., et al., *Crohn's disease among ethnic groups in a large health maintenance organization.* Gastroenterology, 1992. **102**(6): p. 1940-8.
15. Smith, G.D., R. Watson, and D.R. Thompson, *Older people and inflammatory bowel disease: a systematic review.* J Clin Nurs, 2008. **17**(11c): p. 400-6.
16. Charpentier, C., et al., *Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study.* Gut, 2014. **63**(3): p. 423-32.
17. Ha, C.Y. and S. Katz, *Clinical outcomes and management of inflammatory bowel disease in the older patient.* Curr Gastroenterol Rep, 2013. **15**(2): p. 310.
18. Shivashankar, R., et al., *Incidence and Prevalence of Crohn's Disease and Ulcerative Colitis in Olmsted County, Minnesota From 1970 Through 2010.* Clin Gastroenterol Hepatol, 2017. **15**(6): p. 857-863.
19. Hou, J.K., L.A. Feagins, and A.K. Waljee, *Characteristics and Behavior of Elderly-onset Inflammatory Bowel Disease: A Multi-center US Study.* Inflamm Bowel Dis, 2016. **22**(9): p. 2200-5.
20. Ha, C.Y., et al., *Patients with late-adult-onset ulcerative colitis have better outcomes than those with early onset disease.* Clin Gastroenterol Hepatol, 2010. **8**(8): p. 682-687 e1.
21. Ananthakrishnan, A.N., E.L. McGinley, and D.G. Binion, *Inflammatory bowel disease in the elderly is associated with worse outcomes: a national study of hospitalizations.* Inflamm Bowel Dis, 2009. **15**(2): p. 182-9.
22. Vollebregt, P.F., et al., *Validation of Risk Factors for Fecal Incontinence in Patients With Crohn's Disease.* Dis Colon Rectum, 2017. **60**(8): p. 845-851.
23. Subasinghe, D., N.M. Navarathna, and D.N. Samarasekera, *Faecal incontinence and health related quality of life in inflammatory bowel disease patients: Findings from a tertiary care center in South Asia.* World J Gastrointest Pharmacol Ther, 2016. **7**(3): p. 447-52.
24. Norton, C., L.B. Dibley, and P. Bassett, *Faecal incontinence in inflammatory bowel disease: associations and effect on quality of life.* J Crohns Colitis, 2013. **7**(8): p. e302-11.
25. Ananthakrishnan, A.N. and D.G. Binion, *Treatment of ulcerative colitis in the elderly.* Dig Dis, 2009. **27**(3): p. 327-34.

26. Weersma, R.K., et al., *Molecular prediction of disease risk and severity in a large Dutch Crohn's disease cohort.* Gut, 2009. **58**(3): p. 388-95.
27. Hussain, S.W. and D.S. Pardi, *Inflammatory bowel disease in the elderly.* Drugs Aging, 2010. **27**(8): p. 617-24.
28. Ananthakrishnan, A.N., et al., *Differential effect of genetic burden on disease phenotypes in Crohn's disease and ulcerative colitis: analysis of a North American cohort.* Am J Gastroenterol, 2014. **109**(3): p. 395-400.
29. Lang, B.M., et al., *Genetic polymorphisms associated with smoking behaviour predict the risk of surgery in patients with Crohn's disease.* Aliment Pharmacol Ther, 2017.
30. Biedermann, L., et al., *High Rates of Smoking Especially in Female Crohn's Disease Patients and Low Use of Supportive Measures to Achieve Smoking Cessation--Data from the Swiss IBD Cohort Study.* J Crohns Colitis, 2015. **9**(10): p. 819-29.
31. Vavricka, S.R., et al., *High altitude journeys and flights are associated with an increased risk of flares in inflammatory bowel disease patients.* J Crohns Colitis, 2014. **8**(3): p. 191-9.
32. Abegunde, A.T., et al., *Environmental risk factors for inflammatory bowel diseases: Evidence based literature review.* World J Gastroenterol, 2016. **22**(27): p. 6296-317.
33. Claesson, M.J., et al., *Composition, variability, and temporal stability of the intestinal microbiota of the elderly.* Proc Natl Acad Sci U S A, 2011. **108 Suppl 1**: p. 4586-91.
34. O'Toole, P.W. and I.B. Jeffery, *Gut microbiota and aging.* Science, 2015. **350**(6265): p. 1214-5.
35. Ardesia, M., V. Villanacci, and W. Fries, *The aged gut in inflammatory bowel diseases.* Minerva Gastroenterol Dietol, 2015. **61**(4): p. 235-47.
36. Hviid, A., H. Svanstrom, and M. Frisch, *Antibiotic use and inflammatory bowel diseases in childhood.* Gut, 2011. **60**(1): p. 49-54.
37. Kronman, M.P., et al., *Antibiotic exposure and IBD development among children: a population-based cohort study.* Pediatrics, 2012. **130**(4): p. e794-803.
38. Shaw, S.Y., J.F. Blanchard, and C.N. Bernstein, *Association between the use of antibiotics and new diagnoses of Crohn's disease and ulcerative colitis.* Am J Gastroenterol, 2011. **106**(12): p. 2133-42.
39. Murad, Y., et al., *Inflammatory bowel disease in the geriatric population.* Front Biosci (Elite Ed), 2011. **3**: p. 945-54.
40. Fulop, T., et al., *The Role of Immunosenescence in the Development of Age-Related Diseases.* Rev Invest Clin, 2016. **68**(2): p. 84-91.
41. Pawelec, G., *Immunosenenescence: role of cytomegalovirus.* Exp Gerontol, 2014. **54**: p. 1-5.
42. Pinti, M., et al., *Aging of the immune system: Focus on inflammation and vaccination.* Eur J Immunol, 2016. **46**(10): p. 2286-2301.
43. John, E.S., et al., *Management of Inflammatory Bowel Disease in the Elderly.* Curr Treat Options Gastroenterol, 2016. **14**(3): p. 285-304.
44. Swaroop, P.P., *Inflammatory bowel diseases in the elderly.* Clin Geriatr Med, 2007. **23**(4): p. 809-21, vi.
45. Ha, C.Y., *Medical management of inflammatory bowel disease in the elderly: balancing safety and efficacy.* Clin Geriatr Med, 2014. **30**(1): p. 67-78.
46. Singh, M., et al., *Gastrointestinal drug interactions affecting the elderly.* Clin Geriatr Med, 2014. **30**(1): p. 1-15.
47. Parian, A. and C.Y. Ha, *Older age and steroid use are associated with increasing polypharmacy and potential medication interactions among patients with inflammatory bowel disease.* Inflamm Bowel Dis, 2015. **21**(6): p. 1392-400.
48. Frey, B.M. and F.J. Frey, *Clinical pharmacokinetics of prednisone and prednisolone.* Clin Pharmacokinet, 1990. **19**(2): p. 126-46.
49. Taleban, S., et al., *Cancer and inflammatory bowel disease in the elderly.* Dig Liver Dis, 2016. **48**(10): p. 1105-11.
50. Algaba, A., et al., *Incidence, management, and course of cancer in patients with inflammatory bowel disease.* J Crohns Colitis, 2015. **9**(4): p. 326-33.
51. Lemaitre, M., et al., *Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease.* JAMA, 2017. **318**(17): p. 1679-1686.
52. Kornbluth, A., D.B. Sachar, and G. Practice Parameters Committee of the American College of, *Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee.* Am J Gastroenterol, 2010. **105**(3): p. 501-23; quiz 524.

53. Bokemeyer, B., et al., *Mesalazine in left-sided ulcerative colitis: efficacy analyses from the PODIUM trial on maintenance of remission and mucosal healing.* J Crohns Colitis, 2012. **6**(4): p. 476-82.
54. Lichtenstein, G.R., et al., *Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT Registry.* Am J Gastroenterol, 2014. **109**(2): p. 212-23.
55. Akobeng, A.K., et al., *Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease.* Cochrane Database of Systematic Reviews, 2016(9).
56. Taleban, S., *Challenges in the Diagnosis and Management of Inflammatory Bowel Disease in the Elderly.* Curr Treat Options Gastroenterol, 2015. **13**(3): p. 275-86.
57. Nguyen, G.C., L. Sheng, and E.I. Benchimol, *Health Care utilization in elderly onset inflammatory bowel disease: a population-based study.* Inflamm Bowel Dis, 2015. **21**(4): p. 777-82.
58. Schule, S., et al., *Prediction of low bone mineral density in patients with inflammatory bowel diseases.* United European Gastroenterol J, 2016. **4**(5): p. 669-676.
59. Weiler, S., et al., *Treatment of gout in a renal transplant patient leading to severe thrombocytopenia.* J Clin Pharm Ther, 2014. **39**(5): p. 571-2.
60. Afif, W., et al., *Risk factors for lymphoma in patients with inflammatory bowel disease: a case-control study.* Inflamm Bowel Dis, 2013. **19**(7): p. 1384-9.
61. Siegel, C.A., et al., *Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis.* Clin Gastroenterol Hepatol, 2009. **7**(8): p. 874-81.
62. Khan, N., et al., *Risk of lymphoma in patients with ulcerative colitis treated with thiopurines: a nationwide retrospective cohort study.* Gastroenterology, 2013. **145**(5): p. 1007-1015 e3.
63. Kotlyar, D.S., et al., *Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis.* Clin Gastroenterol Hepatol, 2015. **13**(5): p. 847-58 e4; quiz e48-50.
64. Lobaton, T., et al., *Efficacy and safety of anti-TNF therapy in elderly patients with inflammatory bowel disease.* Aliment Pharmacol Ther, 2015. **42**(4): p. 441-51.
65. Ferrante, M., et al., *Predictors of early response to infliximab in patients with ulcerative colitis.* Inflamm Bowel Dis, 2007. **13**(2): p. 123-8.
66. Desai, A., et al., *Older age is associated with higher rate of discontinuation of anti-TNF therapy in patients with inflammatory bowel disease.* Inflamm Bowel Dis, 2013. **19**(2): p. 309-15.
67. Cottone, M., et al., *Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease.* Clin Gastroenterol Hepatol, 2011. **9**(1): p. 30-5.
68. Gomollon, F., et al., *3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management.* J Crohns Colitis, 2017. **11**(1): p. 3-25.
69. Yajnik, V., et al., *Efficacy and Safety of Vedolizumab in Ulcerative Colitis and Crohn's Disease Patients Stratified by Age.* Adv Ther, 2017. **34**(2): p. 542-559.
70. Kawalec, P., et al., *Efficacy and safety of ustekinumab in the induction therapy of TNF-alpha-refractory Crohn's disease patients: a systematic review and meta-analysis.* J Comp Eff Res, 2017.
71. Nguyen, G.C., C.N. Bernstein, and E.I. Benchimol, *Risk of Surgery and Mortality in Elderly-onset Inflammatory Bowel Disease: A Population-based Cohort Study.* Inflamm Bowel Dis, 2017. **23**(2): p. 218-223.
72. Delaney, C.P., et al., *Prospective, age-related analysis of surgical results, functional outcome, and quality of life after ileal pouch-anal anastomosis.* Ann Surg, 2003. **238**(2): p. 221-8.
73. Chapman, J.R., et al., *Ileal pouch-anal anastomosis: does age at the time of surgery affect outcome?* Arch Surg, 2005. **140**(6): p. 534-9; discussion 539-40.
74. Ross, H., et al., *Practice parameters for the surgical treatment of ulcerative colitis.* Dis Colon Rectum, 2014. **57**(1): p. 5-22.
75. Stallmach, A., et al., *Medical and surgical therapy of inflammatory bowel disease in the elderly - prospects and complications.* J Crohns Colitis, 2011. **5**(3): p. 177-88.
76. Ikeuchi, H., et al., *Prognosis following emergency surgery for ulcerative colitis in elderly patients.* Surg Today, 2014. **44**(1): p. 39-43.
77. Shrestha, M.P., J. Ruel, and S. Taleban, *Healthcare maintenance in elderly patients with inflammatory bowel disease.* Ann Gastroenterol, 2017. **30**(3): p. 273-286.
78. Farraye, F.A., et al., *ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease.* Am J Gastroenterol, 2017. **112**(2): p. 241-258.

79. Chaudrey, K., et al., *Updates in vaccination: recommendations for adult inflammatory bowel disease patients.* World J Gastroenterol, 2015. **21**(11): p. 3184-96.
80. Selby, L., et al., *Receipt of preventive health services by IBD patients is significantly lower than by primary care patients.* Inflamm Bowel Dis, 2008. **14**(2): p. 253-8.
81. Neuendorf, R., et al., *Depression and anxiety in patients with Inflammatory Bowel Disease: A systematic review.* J Psychosom Res, 2016. **87**: p. 70-80.
82. Tarricone, I., et al., *Prevalence and effectiveness of psychiatric treatments for patients with IBD: A systematic literature review.* J Psychosom Res, 2017. **101**: p. 68-95.
83. Kok, R.M. and C.F. Reynolds, 3rd, *Management of Depression in Older Adults: A Review.* JAMA, 2017. **317**(20): p. 2114-2122.
84. Card, T., et al., *Hip fractures in patients with inflammatory bowel disease and their relationship to corticosteroid use: a population based cohort study.* Gut, 2004. **53**(2): p. 251-5.
85. Bernstein, C.N., et al., *The incidence of fracture among patients with inflammatory bowel disease. A population-based cohort study.* Ann Intern Med, 2000. **133**(10): p. 795-9.
86. Harbord, M., et al., *The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease.* J Crohns Colitis, 2016. **10**(3): p. 239-54.
87. Schule, S., et al., *Widely differing screening and treatment practice for osteoporosis in patients with inflammatory bowel diseases in the Swiss IBD cohort study.* Medicine (Baltimore), 2017. **96**(22): p. e6788.
88. Juneja, M., et al., *Geriatric inflammatory bowel disease: phenotypic presentation, treatment patterns, nutritional status, outcomes, and comorbidity.* Dig Dis Sci, 2012. **57**(9): p. 2408-15.
89. Annese, V., et al., *European evidence based consensus for endoscopy in inflammatory bowel disease.* J Crohns Colitis, 2013. **7**(12): p. 982-1018.
90. Baars, J.E., et al., *Age at diagnosis of inflammatory bowel disease influences early development of colorectal cancer in inflammatory bowel disease patients: a nationwide, long-term survey.* J Gastroenterol, 2012. **47**(12): p. 1308-22.
91. Shi, H.Y., et al., *Natural History of Elderly-onset Ulcerative Colitis: Results from a Territory-wide Inflammatory Bowel Disease Registry.* J Crohns Colitis, 2016. **10**(2): p. 176-85.